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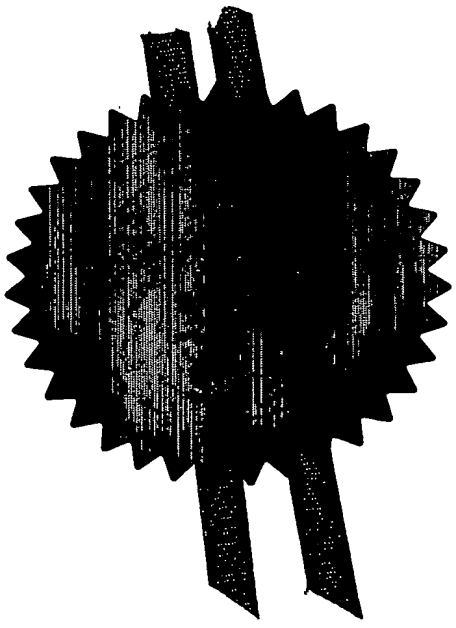

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Dated 22 October 2003

D02934

Patents Form 1/77

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The Patent Office

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Gwent NP9 1RH

1. Your reference — 100864

2. Patent application number *(The Patent Office will fill in this part)* — 0223854.1

3. Full name, address and postcode of the or of each applicant *(underline all surnames)* — AstraZeneca AB
S-151 85 Sodertalje
Sweden

   Patents ADP number *(if you know it)* — 7822448003

   If the applicant is a corporate body, give the country/state of its incorporation — Sweden

4. Title of the invention — THERAPEUTIC TREATMENT

5. Name of your agent *(if you have one)* — Lucy Clare Padget

   "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)* — AstraZeneca UK Limited
Global Intellectual Property
Mereside, Alderley Park
Macclesfield
Cheshire SK10 4TG

   Patents ADP number *(if you know it)* — 7822471002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*
   a) any applicant named in part 3 is not an inventor, or
   b) there is an inventor who is not named as an applicant, or
   c) any named applicant is a corporate body.
   See note (d))

Patents Form 1/77

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Continuation sheets of this form	
Description	11
Claim(s)	02
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Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Authorised Signatory Date 11/10/2002

12. Name and daytime telephone number of person to contact in the United Kingdom: Jennifer C Bennett - 01625 230148

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THERAPEUTIC TREATMENT

The present invention relates to a combination comprising an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, and an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), or a pharmaceutically acceptable salt thereof. This combination is useful in a new method for the treatment or prophylaxis of cancer. The invention also relates to a pharmaceutical composition comprising such a combination and to the use thereof in the manufacture of a medicament for use in the treatment or prophylaxis of prostate cancer.

Cancer affects an estimated 10 million people worldwide. This figure includes incidence, prevalence and mortality. More than 4.4 million cancer cases are reported from Asia, including 2.5 million cases from Eastern Asia, which has the highest rate of incidence in the world. By comparison, Europe has 2.8 million cases, North America 1.4 million cases, and Africa 627,000 cases.

In the UK and US, for example, more than one in three people will develop cancer at some point in their life. Cancer mortality in the U.S. is estimated to account for about 600,000 a year, about one in every four deaths, second only to heart disease in percent of all deaths, and second to accidents as a cause of death of children 1-14 years of age. The estimated cancer incidence in the U.S. is now about 1,380,000 new cases annually, exclusive of about 900,000 cases of non-melanotic (basal and squamous cell) skin cancer.

Cancer is also a major cause of morbidity in the UK with nearly 260,000 new cases (excluding non-melanoma skin cancer) registered in 1997. Cancer is a disease that affects mainly older people, with 65% of cases occurring in those over 65. Since the average life expectancy in the UK has almost doubled since the mid nineteenth century, the population at risk of cancer has grown. Death rates from other causes of death, such as heart disease, have fallen in recent years while deaths from cancer have remained relatively stable. The result is that 1 in 3 people will be diagnosed with cancer during their lifetime and 1 in 4 people will die from cancer. In people under the age of 75, deaths from cancer outnumber deaths from diseases of the circulatory system, including ischaemic heart disease and stroke. In 2000, there were 151,200 deaths from cancer. Over one fifth (22 per cent) of these were from lung cancer, and a quarter (26 per cent) from cancers of the large bowel, breast and prostate.

Worldwide, the incidence and mortality rates of certain types of cancer (of stomach, breast, prostate, skin, and so on) have wide geographical differences which are attributed to

racial, cultural, and especially environmental influences. There are over 200 different types of cancer but the four major types, lung, breast, prostate and colorectal, account for over half of all cases diagnosed in the UK and US. Prostate cancer is the fourth most common malignancy among men worldwide, with an estimated 400,000 new cases diagnosed annually, accounting for 3.9 percent of all new cancer cases.

Current options for treating cancers include surgical resection, external beam radiation therapy and / or systemic chemotherapy. These are partially successful in some forms of cancer, but are not successful in others. There is a clear need for new therapeutic treatments.

Recently, endothelin A receptor antagonists have been identified as potentially of value in the treatment of cancer (Cancer Research, 56, 663-668, February 15th, 1996 and Nature Medicine, Volume 1, Number 9, September 1999, 944-949).

The endothelins are a family of endogenous 21 amino acid peptides comprising three isoforms, endothelin-1, endothelin-2 and endothelin-3. The endothelins are formed by cleavage of the Trp^{21}-Val^{22} bond of their corresponding proendothelins by an endothelin converting enzyme. The endothelins are among the most potent vasoconstrictors known. They exhibit a wide range of other activities including stimulation of cell proliferation and mitogenesis, inhibition of apoptosis, extravasation and chemotaxis, and also interact with a number of other vasoactive agents.

The endothelins are released from a range of tissue and cell sources including vascular endothelium, vascular smooth muscle, kidney, liver, uterus, airways, intestine and leukocytes. Release can be stimulated by hypoxia, shear stress, physical injury and a wide range of hormones and cytokines. Elevated endothelin levels have been found in a number of disease states in man including cancers.

In recent years it has been discovered that certain growth factor tyrosine kinase enzymes are important in the transmission of biochemical signals which initiate cell replication. They are large proteins which span the cell membrane and possess an extracellular binding domain for growth factors such as epidermal growth factor (EGF) and an intracellular portion which functions as a kinase to phosphorylate tyrosine amino acids in proteins and hence to influence cell proliferation.

Various classes of receptor tyrosine kinases are known (Wilks, Advances in Cancer Research, 1993, 60, 43-73) based on families of growth factors which bind to different receptor tyrosine kinases. The classification includes Class I receptor tyrosine kinases comprising the EGF family of receptor tyrosine kinases such as the EGF, TGFα, NEU, erbB,

Xmrk, HER and let23 receptors, Class II receptor tyrosine kinases comprising the insulin family of receptor tyrosine kinases such as the insulin and IGFI receptors and insulin-related receptor (IRR) and Class III receptor tyrosine kinases comprising the platelet-derived growth factor (PDGF) family of receptor tyrosine kinases such as the PDGFα, PDGFβ and colony-stimulating factor 1 (CSF1) receptors.

It is known that Class I kinases such as the EGF family of receptor tyrosine kinases are frequently present in common human epithelial cancers such as cancer of the prostate (Visakorpi *et al.*, Histochem. J., 1992, 24, 481). Accordingly it has been recognised that an inhibitor of receptor tyrosine kinases should be of value as a selective inhibitor of the growth of certain carcinomas.

It has been previously demonstrated that stimulation of rat-1 fibroblast cells with endothelin-1 resulted in transactivation of the EGFR *in vitro* (Daub, H et al., Nature, 1996, 379:557). Since both the endothelin and EGFR systems play a role in carcinogenesis the present inventors investigated the potential for the combined use of endothelin antagonists and EGFR TKIs for the treatment of cancer. The present inventors have unexpectedly found that the combination use of particular endothelin receptor antagonists, or pharmaceutically acceptable salts thereof, and particular EGFR TKIs, or pharmaceutically acceptable salts thereof, can have a synergistic and or additive effect in the treatment of cancer.

Therefore according to the present invention, there is provided a combination, comprising an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, and an EGFR TKI, or a pharmaceutically acceptable salt thereof.

Herein, where the term "combination" is used it is to be understood that this refers to simultaneous, separate or sequential administration. In one aspect of the invention "combination" refers to simultaneous administration. In another aspect of the invention "combination" refers to separate administration. In a further aspect of the invention "combination" refers to sequential administration. Where the administration is sequential or separate, the delay in administering the second component should not be such as to lose the benefit of the synergistic effect of the combination.

Where cancer is referred to, particularly it refers to oesophageal cancer, myeloma, hepatocellular, pancreatic, cervical cancer, ewings tumour, neuroblastoma, kaposis sarcoma, ovarian cancer, breast cancer, colorectal cancer, prostate cancer, bladder cancer, melanoma, lung cancer - non small cell lung cancer (NSCLC), and small cell lung cancer (SCLC), gastric cancer, head and neck cancer, brain cancer, renal cancer, lymphoma and leukaemia. More

particularly it refers to prostate cancer. In addition, more particularly it refers to SCLC, NSCLC, colorectal cancer, ovarian cancer and / or breast cancer. Furthermore, more particularly it refers to bladder cancer, oesophageal cancer, gastric cancer, melanoma, cervical cancer and / or renal cancer. In another embodiment of the invention, particularly the cancer is in a metastatic state, and more particularly the cancer produces metastases to the bone. In a further embodiment of the invention, particularly the cancer is in a metastatic state, and more particularly the cancer produces skin metastases.

Where the treatment of cancer is referred to particularly this is the treatment of cancerous tumours expressing both endothelin A and EGFR. This treatment is in terms of one or more of the extent of the response, the response rate, the time to disease progression and the survival rate. It is further expected that the combination use of particular endothelin receptor antagonists, or pharmaceutically acceptable salts thereof, and particular EGFR TKIs, or pharmaceutically acceptable salts thereof, will have a beneficial effect in preventing the onset of cancer in warm-blooded animals, such as man.

Suitable compounds, or a pharmaceutically acceptable salt thereof, possessing endothelin receptor antagonist activity include those described in US 5292740, US 5334598, US 5378715, US 5389620, US 5420123, US 5464853, US 5482960, US 5514691, US 5514696, US 5541186, US5543521, US 5559105, US 5571821, US 5780473, US 5962490, US 5965732, US 6080774, US 6420567, US 2002091272(A1), WO 93/08799, WO 93/21219, WO 93/23404, WO 93/25580, WO 94/02474, WO 94/03483, WO 94/14434, WO 94/21259, WO 94/21590, WO 94/24084, WO 94/25013, WO 94/27979, WO 95/03044, WO 95/03295, WO 95/04530, WO 95/04534, WO 95/05372, WO 95/05374, WO 95/05376, WO 95/08989, WO 95/12611, WO 95/13262, WO 95/15944, WO 95/15963, WO 96/20177, WO 95/26360, WO 95/26716, WO 95/26360, WO95/26957, WO 95/33748, WO 95/33752, WO 95/35107, WO 96/04905, WO 96/06095, WO 96/07653, WO 96/08483, WO 96/08486, WO 96/08487, WO 96/09818, WO 96/11914, WO 96/11927, WO 96/12706, WO 96/15109, WO 96/19455, WO 96/19459, WO 96/22978, WO 96/23773, WO 96/30358, WO 96/31492, WO 96/33170, WO 96/33190, WO96/40681, WO 97/30045, WO 98/09953, WO 95/08550, WO 98/49162, WO 99/06397, WO 01/49685, WO 02/64573, EP 436189, EP 496452, EP 510526, EP 526708, EP 552417, EP 555537, EP 601386, EP 617001, EP 628569, EP 633259, EP 658548, EP 682016, EP 713875, EP 702012, EP 733626, EP 743307, EP 749964, GB2266890, GB 2275926, GB 2276383, GB 2277446, GB 2295616, DE 4341663, JP 6256261, JP 6122625, JP 7330622, JP 7133254, JP 8059635, JP 7316188, and JP 7258098 and the receptor

antagonists described therein, particularly those described in claim 1 and the named examples, of the above patents and applications, are incorporated herein by reference.

Additional suitable compounds, or a pharmaceutically acceptable salt thereof, possessing endothelin receptor antagonist activity include those described in the J Med Chem papers **1996**, *39*, 2123-2128; **1997**, *40*, 3, 322-330; **2001**, *44*, 1211-1216; **2001**, *44*, 3978-3984 and the endothelin receptor antagonists described therein are also incorporated herein by reference.

Further suitable compounds, or a pharmaceutically acceptable salt thereof, possessing endothelin receptor antagonist activity include A-127722, atrasentan (ABT-627), BQ-123, BQ-788, BMS 182874, feloprentan (BSF 420627), FR139317, IPI-950, L-749,329, L-754,142, LU 110896, LU 110897, PD 156707, PD 155080, Ro 46-2005, bosentan (Ro 47-0203), SB 217242, SB 209670, TAK-044, YM598, sitaxsentan (TBC11251), ambrisentan, tezosentan, darusentan, *N*-[[2'-[[(4,5-dimethyl-3-isoxazolyl)amino]sulphonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl]methyl]-*N*,3,3-trimethylbutanamide, ZD1611 and *N*-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide (ZD4054).

A particular compound possessing endothelin receptor antagonist activity is atrasentan (ABT-627) or a pharmaceutically acceptable salt thereof. A particular compound possessing endothelin receptor antagonist activity is YM598 or a pharmaceutically acceptable salt thereof. A particular compound possessing endothelin receptor antagonist activity is ZD4054 or a pharmaceutically acceptable salt thereof. A particular compound possessing endothelin receptor antagonist activity is ZD1611 or a pharmaceutically acceptable salt thereof.

In another aspect of the invention the endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, is an endothelin A receptor antagonist. In a further aspect of the invention, the endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, is an endothelin B receptor antagonist. In an additional aspect of the invention, the endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, is a mixed endothelin A and B receptor antagonist.

Suitable compounds, or a pharmaceutically acceptable salt thereof, possessing EGFR TKI activity include those described in EP 0566226, EP 0787722, WO 96/30347, WO 96/33980, WO 97/02266, WO 97/30034, WO 97/38983, WO 98/50038, WO 99/09016, WO 99/24037, WO 99/55683, Nature Medicine, 2000, 6, 1024-1028 and US 6,002,008 and these

EGFR TKIs, particularly those of claim 1 and the named examples of these patents and applications, are incorporated herein by reference.

Particular classes of EGFR TKIs are the quinazolines, or a pharmaceutically acceptable salt thereof.

Particular compounds, or pharmaceutically acceptable salts thereof possessing EGFR TKI activity include:

N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (ZD1839);

N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine, or a pharmaceutically-acceptable salt thereof (linked to the code numbers CP 358774 and OSI-774 (the monomethanesulphonate salt));

6-acrylamido-*N*-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (linked to the code numbers PD 183805 and CI 1033);

4-[(1R)-1-phenylethylamino]-6-(4-hydroxyphenyl)-7H-pyrrolo[2,3-*d*]pyrimidine (linked to the code numbers PKI-166, CGP 75166 and CGP 59326);

N-[4-(3-bromoanilino)quinazolin-6-yl]but-2-ynamide (linked to the code numbers CL-387785 and EKB-785); and

4-(3-chloro-4-fluoroanilino)-3-cyano-6-(4-dimethylaminobut-2(E)-enamido)-7-ethoxyquinoline (EKB-569).

Further particular compounds, or pharmaceutically acceptable salts thereof, possessing EGFR TKI activity include ZD1839, CP 358774, CI 1033, PKI-166, CL-387785 and EKB-569. Particularly the compound, or a pharmaceutically acceptable salt thereof, possessing EGFR TKI activity is ZD1839 or CP 358774. More particularly the compound, or a pharmaceutically acceptable salt thereof, possessing EGFR TKI activity is ZD1839.

Particular combinations of the present invention include:

- ZD4054, or a pharmaceutically acceptable salt thereof, and ZD1839, or a pharmaceutically acceptable salt thereof;
- ZD4054, or a pharmaceutically acceptable salt thereof, and CP 358774, or a pharmaceutically acceptable salt thereof;
- ZD1611, or a pharmaceutically acceptable salt thereof, and ZD1839, or a pharmaceutically acceptable salt thereof;
- ZD1611, or a pharmaceutically acceptable salt thereof, and CP 358774, or a pharmaceutically acceptable salt thereof;

- atrasentan, or a pharmaceutically acceptable salt thereof, and ZD1839, or a pharmaceutically acceptable salt thereof;
- atrasentan, or a pharmaceutically acceptable salt thereof, and CP 358774, or a pharmaceutically acceptable salt thereof;
- YM598, or a pharmaceutically acceptable salt thereof, and ZD1839, or a pharmaceutically acceptable salt thereof; and
- YM598, or a pharmaceutically acceptable salt thereof, and CP 358774, or a pharmaceutically acceptable salt thereof.

Suitable pharmaceutically-acceptable salts include, for example, salts with alkali metal (such as sodium, potassium or lithium), alkaline earth metals (such as calcium or magnesium), ammonium salts, and salts with organic bases affording physiologically acceptable cations, such as salts with methylamine, dimethylamine, trimethylamine, piperidine and morpholine. In addition, for those compounds which are sufficiently basic, suitable pharmaceutically-acceptable salts include, pharmaceutically-acceptable acid-addition salts with hydrogen halides, sulphuric acid, phosphoric acid and with organic acids such as citric acid, maleic acid, methanesulphonic acid and p-toluenesulphonic acid. Alternatively, the compounds may exist in zwitterionic form.

The therapeutic effect (for example effects on cell proliferation and / or the effect on cell survival or induction of an apoptotic response) of the combination may be tested *in vitro* by the application of an endothelin receptor antagonists and a EGFR TKI to human carcinoma cell cultures expressing both endothelin A and EGFR.

Therefore according to the present invention, there is provided a combination, comprising an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, and an EGFR TKI, or a pharmaceutically acceptable salt thereof for use as a medicament.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, and an EGF TKI, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier, in combination with a pharmaceutical composition which comprises an EGF TKI, or a

pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier.

Therefore according to the present invention, there is provided a method of treating cancer, in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof in combination with an effective amount of an EGF TKI, or a pharmaceutically acceptable salt thereof.

According to a further aspect of the present invention there is provided a kit comprising an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, and an EGF TKI, or a pharmaceutically acceptable salt thereof; optionally with instructions for use.

According to a further aspect of the present invention there is provided a kit comprising:

a) an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, in a first unit dosage form;

b) an EGF TKI, or a pharmaceutically acceptable salt thereof; in a second unit dosage form; and

c) container means for containing said first and second dosage forms; and optionally

d) with instructions for use.

According to a further aspect of the present invention there is provided a kit comprising:

a) an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;

b) an EGF TKI, or a pharmaceutically acceptable salt thereof, in a second unit dosage form; and

c) container means for containing said first and second dosage forms; and optionally

d) with instructions for use.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, and an EGF TKI, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier for use in the treatment of cancer.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier, in combination with a pharmaceutical composition which comprises an EGF TKI, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier for use in the treatment of cancer.

The pharmaceutical compositions may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. In general the above compositions may be prepared in a conventional manner using conventional excipients.

According to a further aspect of the present invention there is provided a kit comprising an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, and an EGF TKI, or a pharmaceutically acceptable salt thereof; optionally with instructions for use; for use in the treatment of cancer.

According to a further aspect of the present invention there is provided a kit comprising:

a) an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, in a first unit dosage form;

b) an EGF TKI, or a pharmaceutically acceptable salt thereof; in a second unit dosage form; and

c) container means for containing said first and second dosage forms; and optionally

d) with instructions for use;

for use in the treatment of cancer.

According to a further aspect of the present invention there is provided a kit comprising:

a) an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;

b) an EGF TKI, or a pharmaceutically acceptable salt thereof, in a second unit dosage form; and

c) container means for containing said first and second dosage forms; and optionally

d) with instructions for use;

for use in the treatment of cancer.

According to another feature of the invention there is provided the use of an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, in combination with an EGF TKI, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of cancer, in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, in combination with an EGF TKI, or a pharmaceutically acceptable salt thereof, in the treatment of cancer, in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination comprising an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, and an EGF TKI, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable diluent or carrier, in combination with an effective amount of an EGF TKI, or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment for use in the treatment of cancer.

The endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, will normally be administered to a warm-blooded animal at a unit dose of 1g or less daily and this would be expected to provide a therapeutically-effective dose. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

The EGF TKI, or pharmaceutically acceptable salt thereof, will normally be administered to a warm-blooded animal at a unit dose, for example, from about 20 mg to 1 g of active ingredient. When the EGFR TKI is ZD1839, a conventional tablet formulation may be used for oral administration containing 50 mg, 100 mg, 250 mg or 500 mg of active ingredient. Conveniently the daily oral dose of ZD1839 is above 150 mg, for example, in the range 150 to 750 mg, preferably in the range 200 to 500 mg. For a single dosage form, the active ingredients may be compounded with an appropriate and convenient amount of

excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 20 mg to about 500 mg of each active ingredient. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

The dosage of each of the two drugs and their proportions have to be composed so that the best possible treatment effects, as defined by national and international guidelines (which are periodically reviewed and re-defined), will be met.

Claims

1. A combination, comprising an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, and an EGFR TKI, or a pharmaceutically acceptable salt thereof.

2. A combination according to claim 1 wherein the endothelin receptor antagonist is selected from A-127722, atrasentan (ABT-627), BQ-123, BQ-788, BMS 182874, feloprentan (BSF 420627), FR139317, IPI-950, L-749,329, L-754,142, LU 110896, LU 110897, PD 156707, PD 155080, Ro 46-2005, bosentan (Ro 47-0203), SB 217242, SB 209670, TAK-044, YM598, sitaxsentan (TBC11251), ambrisentan, tezosentan, darusentan, *N*-[[2'-[[(4,5-dimethyl-3-isoxazolyl)amino]sulphonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl]methyl]-*N*,3,3-trimethylbutanamide, ZD1611 and *N*-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide (ZD4054), or a pharmaceutically acceptable salt thereof.

3. A combination according to claim 1 or 2 wherein the EGFR TKI is selected from:
N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (ZD1839);
N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine, or a pharmaceutically-acceptable salt thereof (linked to the code numbers CP 358774 and OSI-774 (the monomethanesulphonate salt));
6-acrylamido-*N*-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (linked to the code numbers PD 183805 and CI 1033);
4-[(1R)-1-phenylethylamino]-6-(4-hydroxyphenyl)-7H-pyrrolo[2,3-*d*]pyrimidine (linked to the code numbers PKI-166, CGP 75166 and CGP 59326);
N-[4-(3-bromoanilino)quinazolin-6-yl]but-2-ynamide (linked to the code numbers CL-387785 and EKB-785); and
4-(3-chloro-4-fluoroanilino)-3-cyano-6-(4-dimethylaminobut-2(E)-enamido)-7-ethoxyquinoline (EKB-569);
or a pharmaceutically acceptable salt thereof.

4. A combination according to any one of claims 1-3 wherein the endothelin receptor antagonist is selected from ZD4054, or a pharmaceutically acceptable salt thereof, and the EGFR TKI is selected from ZD1839, or a pharmaceutically acceptable salt thereof.

5. A combination according to any one of claims 1-4 for use as a medicament.

6. A pharmaceutical composition comprising a combination according to any one of claims 1-4, in association with a pharmaceutically acceptable diluent or carrier.

7. A method of treating cancer, in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a combination according to any one of claims 1-4.

8. The use of a combination according to claims 1-4, in the manufacture of a medicament for use in the treatment of cancer, in a warm-blooded animal, such as man.

9. A combination comprising a combination according to claims 1-4, for use in the treatment of cancer.

10. The method or use according to claims 7-9 wherein the cancer is oesophageal cancer, myeloma, hepatocellular, pancreatic, cervical cancer, ewings tumour, neuroblastoma, kaposis sarcoma, ovarian cancer, breast cancer, colorectal cancer, prostate cancer, bladder cancer, melanoma, lung cancer - non small cell lung cancer (NSCLC), and small cell lung cancer (SCLC), gastric cancer, head and neck cancer, brain cancer, renal cancer, lymphoma and leukaemia.

ABSTRACT

TITLE: THERAPEUTIC TREATMENT

A combination, comprising an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, and an EGFR TKI, or a pharmaceutically acceptable salt thereof is described.

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